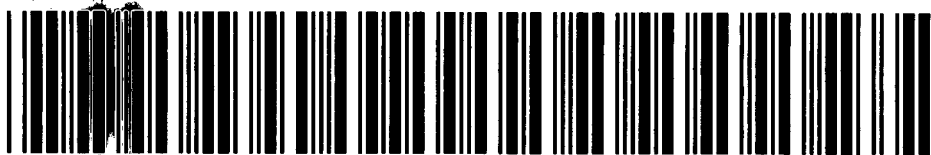


IDS REFERENCES



FOR

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/087062 A3(51) International Patent Classification⁷: C07D 231/12, 401/04, 307/46, 263/38, 277/34, 261/08, A61K 31/34, 31/415, 31/42, 31/425, 31/44, A61P 29/00

(74) Agents: SUBRAMANIAM, Hariharan et al.; Subramaniam, Nataraj and Associates, E-556 Greater Kailash II, New Delhi 110 048, Maharashtra (IN).

(21) International Application Number: PCT/IN03/00133

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 1 April 2003 (01.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
327/MUM/2002 5 April 2002 (05.04.2002) IN(71) Applicant (*for all designated States except US*): CADILA HEALTHCARE LIMITED [IN/IN]; Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat (IN).(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): LOHRAY, Braj, Bhushan [IN/IN]; Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat (IN). LOHRAY, Vidya, Bhushan [IN/IN]; Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat (IN). JAIN, Mukul, R. [IN/IN]; Zydus Towers, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India (IN). PATEL, Gautam, D. [IN/IN]; Zydus Towers, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India (IN). PINGALI, Harikishore [IN/IN]; Zydus Towers, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India (IN).

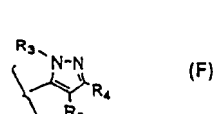
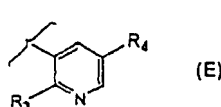
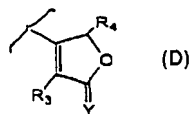
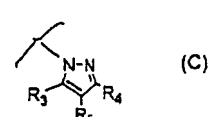
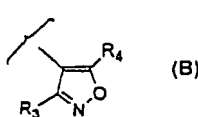
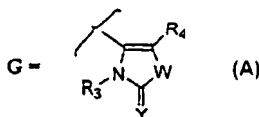
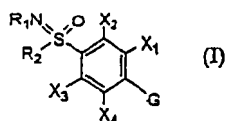
Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
20 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 4-(HETEROCYCLYL)-BENZENESULFOXIMINE COMPOUNDS FOR THE TREATMENT OF INFLAMMATION



(57) Abstract: The present invention describes novel compounds of formula (I) having antiinflammatory activity, process for their preparation and pharmaceutical composition containing them.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 03/00133

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/12 C07D401/04 C07D307/46 C07D263/38 C07D277/34
 C07D261/08 A61K31/34 A61K31/415 A61K31/42 A61K31/425
 A61K31/44 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PUIG, CARLES ET AL: "Synthesis and Biological Evaluation of 3,4-Diaryloxazolones: A New Class of Orally Active Cyclooxygenase-2 Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY (2000), 43(2), 214-223, XP002251891 chart 1, p.214; Table 1, p.217</p> <p style="text-align: center;">--- -/--</p>	1-21

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

8 September 2003

Date of mailing of the international search report

22/09/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Schuemacher, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 03/00133

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PENNING, THOMAS D. ET AL: "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-'5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib" JOURNAL OF MEDICINAL CHEMISTRY (1997), 40(9), 1347-1365, XP002114833 the whole document	1-21
A	SHIN, S. S. ET AL: "2,2-Dimethyl-4,5-diaryl-3(2H)furanone derivatives as selective cyclo-oxygenase-2 inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2001), 11(2), 165-168, XP004314839 the whole document	1-21
A	FRIESEN, RICHARD W. ET AL: "2-Pyridinyl-3-'4-(methylsulfonyl) phenyl pyridines: selective and orally active cyclooxygenase -2 inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (1998), 8(19), 2777-2782, XP004139619 compounds 1-3, p.2777 table 1	1-21
Y	US 6 020 343 A (BELLEY, MICHEL ET AL) 1 February 2000 (2000-02-01) claims 1,37-42	1-21
A	US 5 859 257 A (TALLEY, JOHN J.) 12 January 1999 (1999-01-12) column 95 -column 98; claim 1	1-21
Y	WO 01 083475 A (J. URIACH & CIA S.A., SPAIN) 8 November 2001 (2001-11-08) claims 1,4,11-15	1-21
Y,P	EP 1 251 126 A (PHARMACIA CORPORATION, USA) 23 October 2002 (2002-10-23) claims 1,5-7,113-117	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00133

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-12, 17 and 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 03/00133

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5859257	A	RU 2200158 C2	10-03-2003
		WO 9625405 A1	22-08-1996
		US 5985902 A	16-11-1999
		ZA 9601150 A	12-02-1997

WO 01083475	A 08-11-2001	ES 2166710 A1	16-04-2002
		AU 4838201 A	12-11-2001
		BR 0110328 A	07-01-2003
		CA 2407418 A1	08-11-2001
		EP 1281709 A1	05-02-2003
		WO 0183475 A1	08-11-2001
		NO 20025101 A	20-12-2002
		US 2003114456 A1	19-06-2003

EP 1251126	A 23-10-2002	EP 1251126 A2	23-10-2002
		US 2003032657 A1	13-02-2003
		US 2003149078 A1	07-08-2003

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1 relates to an extremely large number of possible compounds. In fact, the claim contains so many options, particularly due to the use of the terms "their analogs, their derivatives" that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible.

Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the compounds of formula (I) according to claim 1, for which G is A, B, C, D, E and F and those compounds recited in the examples of the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

PATENT COOPERATION TREATY

PCT



REC'D 13 JUL 2004

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZRC-MC-004	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/IN 03/00133	International filing date (day/month/year) 01.04.2003	Priority date (day/month/year) 05.04.2002
International Patent Classification (IPC) or both national classification and IPC C07D231/12		
Applicant CADILA HEALTHCARE LIMITED et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>		
Date of submission of the demand 30.10.2003	Date of completion of this report 12.07.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schuemacher, A Telephone No. +49 89 2399-7818 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IN 03/00133

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-74 as originally filed

Claims, Numbers

1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IN 03/00133

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1 (part) 9-12, 17, 18

because:

☒ the said international application, or the said claims Nos. 9-12, 17, 18 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1 (part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-21
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-21
Industrial applicability (IA)	Yes: Claims	1-8,13-16,18-21
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 9-12, 17 and 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

As already indicated in the search report (see Box I, 08.09.2003), a meaningful search covering the subject-matter of present claim 1 was impossible. The search was limited to compounds of formula (I) according to claim 1 **with the exception of any of their "analogs and their derivatives"**. Since a complete search has not been carried out, any statements made in this communication with respect to novelty and inventive step are thus made in the light of those claims which were searched completely.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: Journal Of Medicinal Chemistry (2000), 43(2), 214-223
- D2: Journal Of Medicinal Chemistry (1997), 40(9), 1347-1365
- D3: Bioorganic & Medicinal Chemistry Letters (2001), 11(2), 165-168
- D4: Bioorganic & Medicinal Chemistry Letters (1998), 8(19), 2777-2782
- D5: US-A-6020343
- D6: US-A-5859257
- D7: WO-A-01083475

1. Novelty, Article 33(2) PCT:

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e 4-(heterocyclyl)-phenylsulfoximine compounds useful for the treatment of inflammatory diseases, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT:

The prior art documents relate to 4-(heterocyclyl)-benzenesulfonamide compounds also useful for the treatment of inflammation but which differ from the claimed compounds on account of the sulfonamide group instead of a **sulfoximine** group.

Moreover D5 discloses generically in its claim 1 the compounds which are disclaimed from

the scope of present claim 1 by a proviso "when G is "D", then at least one of X¹-X⁴ is not hydrogen". Additionally, D5 does not contain specific examples of compounds with the sulfoximine group, i.e specific examples of compounds falling within the scope of present claim 1; thus, D5 does not take away the novelty of the subject-matter of the present application.

2. Inventive step, Article 33(3) PCT:

The Applicant appears to have set himself the task of making available further compounds useful for the treatment of inflammatory disease, TNF- α mediated diseases, cyclooxygenase related diseases like inflammation and pain (see p.4, I.4-6).

D5, considered to represent the most relevant state of the art, discloses 4-heterocyclyl-benzenesulfoximine derivatives, especially compounds wherein the heterocyclic part is furan-2-one (see claim 1 of D5) , which are explicitly disclaimed from the scope of present claim 1 by a proviso.

According to the Applicant's letter dated the 29.06.2004, the inventiveness of the present application lies in the combination of a heterocyclic part with an alkylsulfoximine group. It is clear from the teaching of claim 4 of D7 that the heterocyclic part of these molecules (in D5, the furan-2-one ring) can also be replaced by a pyrazole, an isoxazole, an oxazole, an imidazole or an oxazolone ring. Consequently, the skilled person, looking for further anti-inflammatory agents would combine the teaching of D7 with the compounds of D5 and arrive without inventive skills to the presently claimed compounds.

Consequently, D5 can already be considered to provide a solution to the above mentioned technical problem and the new technical problem underlying the present application has therefore to be seen in the provision of anti-inflammatory agents with **unexpected advantageous effect** compared to the structurally closest compounds, in order to show convincingly that the surprising effect is indeed due to the distinguishing feature, namely the alkylsulfoximine group.

The current application contains pharmacological data proving the alleged activity on p.40, and in his letter of 29.06.04, the Applicant stated also that the current compounds does not present the drawbacks of the known anti-inflammatory agents, namely the side-effects of ulcerogenicity or cardiac problems. The claimed compounds are therefore better anti-inflammatory agents than those from the prior art and an inventive step could in principle be acknowledged for those compounds which indeed provide such surprising effects. However, it is considered that the claims should only represent a reasonable generalisation over the examples, such that all compounds falling within the scope of the claims provide a solution to the problem. If as stated in the Applicant's letter, the combination of an

the scope of present claim 1 by a proviso "when G is "D", then at least one of X¹-X⁴ is not hydrogen". Additionally, D5 does not contain specific examples of compounds with the sulfoximine group, i.e specific examples of compounds falling within the scope of present claim 1; thus, D5 does not take away the novelty of the subject-matter of the present application.

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IN 03/00133

alkylsulfoximine with a heterocycle confers inventiveness over the prior art, only such compounds could be claimed. However in the view of the examples provided, it appears that another essential structural feature is that R^3 is a substituted phenyl ring.

At present, it does not appear scientifically reasonable that all compounds of claim 1 possess the desired activity: the generic and open-ended terms "substituted or unsubstituted" or the extremely large number of different groups that can be X^1 - X^4 and R^3 - R^5 (R^1 should definitively be limited to alkyl) are certainly not considered to be appropriate and moreover not supported by the description, wherein all examples of compounds have e.g X^1 - X^4 limited to a hydrogen or fluor atom and R^3 limited to a substituted phenyl ring. The criteria of Article 33(3) PCT in conjunction with Articles 5 and 6 PCT are therefore not considered to be satisfied.

3. industrial applicability:

For the assessment of the present claims 9-12, 17 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 03/00133

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6020343	A	01-02-2000	US 6169188 B1	02-01-2001
			US 5981576 A	09-11-1999
			AT 229515 T	15-12-2002
			AU 703871 B2	01-04-1999
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